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In This Issue

The Role of Aldosterone Antagonists in Systolic Heart Failure

The development of new drugs for the treatment of systolic heart failure (HF) continues to be a high priority because of the devastating consequences of this disease. An estimated five million Americans have symptomatic HF with 550,000 new cases diagnosed annually.[1] HF is a primary or contributing cause in over 265,000 deaths annually and is associated with a 5-year mortality rate of approximately 50%.

The total annual costs for the care of HF patients in the United States are estimated to be over $25 billion.[1] An estimated one million HF hospitalizations each year cost approximately $6000 to 12,000 per admission.[2] Repeat hospitalizations are common, with 3-month readmission rates ranging from 20 to 50%.[3] Among those 65 years of age or older, HF is the largest and most expensive diagnosis-related group (DRG) in the United States. In 1999, Medicare paid beneficiaries $3.6 million for HF treatment.

Therapeutic goals for HF include improving survival and reducing the significant morbidity and associated impairment in quality of life. This article will provide an overview of the role of aldosterone antagonists in HF and describe recent studies that evaluated the impact of these drugs on patient outcomes.

Changing Paradigm of HF

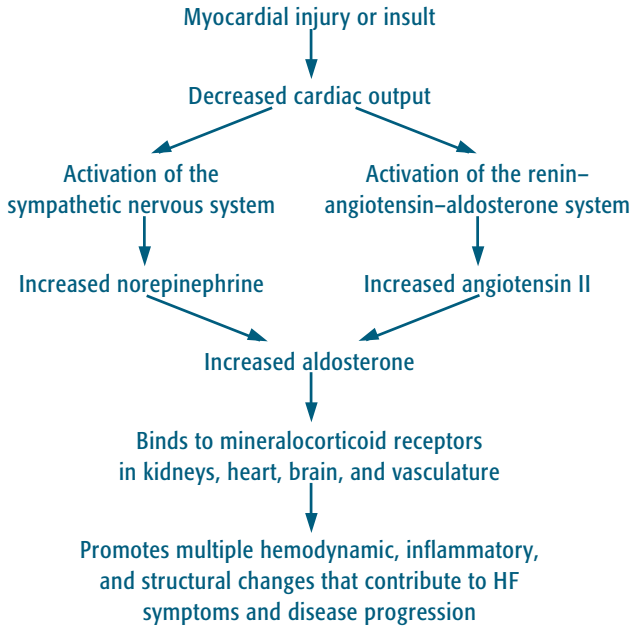
Historically, HF was viewed as a primarily hemodynamic disorder characterized by poor cardiac contractility leading to sodium and water retention. The drugs of choice were inotropic drugs such as digoxin and diuretics to control edema-related symptoms. Today, HF is understood to be a complex syndrome involving neurohormonal activation, inflammation, and cardiac remodeling.[4] Research has demonstrated that chronic activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) plays a central role in the progression of HF (see Figure 1). This greater understanding of the pathophysiology of HF has led to more sophisticated approaches to drug therapy, which specifically block the detrimental effects of neurohormonal activation and slow progression of the disease.

The current standard of care for HF is based on combination drug therapy, including beta blockers and angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).[5,6] These drugs reduce HFrelated morbidity by blocking the harmful effects of chronic elevations in norepinephrine, angiotensin II, and aldosterone. More recently, this therapeutic approach has been expanded to include the use of specific aldosterone antagonists.

Role of Aldosterone in HF

Aldosterone is a mineralocorticoid and a major effector hormone of the RAAS.[7–9] Aldosterone plays a physiologic role in maintaining circulatory homeostasis to prevent excessive water and salt loss. Stimuli for aldosterone release include reductions in intravascular volume, decreased renal perfusion, water or sodium loss, and excess potassium. Angiotensin II is a major hormonal stimulus for aldosterone production.[7,8] Other stimuli include corticotropin, norepinephrine, endothelin, vasopressin, and serotonin. The renal effects of aldosterone are mediated through binding with mineralocorticoid receptors in the distal nephron.

Figure 1: Role of Neurohormonal Activation in the Cycle of Heart Failure



Although it was once thought that aldosterone was produced solely by the adrenal cortex, it is now known that local aldosterone is produced by endothelial and smooth muscle cells in the heart, brain, and vasculature.[7] In fact, early studies suggest that aldosterone production in the heart following myocardial infarction (MI) may contribute to tissue repair.[10]

Aldosterone appears to have multiple actions that contribute to the pathophysiology of HF (see Table 1).[7–9] Plasma concentrations of aldosterone may increase to 20 times normal in patients with HF due to increased production and decreased hepatic clearance.[11] Increased secretion of aldosterone contributes to sodium retention, expansion of the intravascular volume, and edema. More importantly, however, aldosterone promotes cardiac and vascular remodeling, collagen deposition, and eventually fibrosis within the heart, kidneys, and vasculature.[7-9,11] Sustained elevations of both angiotensin II and aldosterone cause endothelial dysfunction, abnormal vasomotor reactivity and impaired baroreceptor responsiveness.

Ventricular remodeling, which is triggered by prolonged neurohormonal activation and possibly genetic factors, leads to hypertrophy and changes in the size, shape, and function of the ventricle. Key components of the remodeling process are increased collagen synthesis, loss of myocytes, and interstitial fibrosis — which are promoted by increased aldosterone. Although ACEIs and ARBs blunt the production of aldosterone initially, concentrations may return to baseline with continued therapy.[12,13] In an attempt to overcome this "aldosterone escape," studies have examined the potential role of specific aldosterone antagonists in patients with HF.

Available Aldosterone Blockers

Currently, two aldosterone antagonists are approved by the Food and Drug Administration (FDA) for HF treatment. Both of these drugs antagonize the effects of aldosterone by competitive binding to mineralocorticoid receptors in the kidney, heart, brain, and vasculature. For many years before it was approved for HF treatment, spironolactone was used in cardiovascular patients as a diuretic with potassium-sparing properties.[14]

Spironolactone undergoes hepatic metabolism to multiple metabolites, including canrenone, which has a half-life of 12 to 20 hours and is largely responsible for the drug's mineralocorticoid actions. The drug is a non-selective aldosterone antagonist that binds to mineralocorticoid receptors and other steroid receptors. Binding to progesterone and androgen receptors is believed to be responsible for the drug's sex-hormone related adverse effects, including gynecomastia, impotence, breast pain, and menstrual irregularities.[9,14]

Eplerenone is the first selective aldosterone antagonist to receive FDA approval.[9] Eplerenone is chemically derived from spironolactone by inserting a 9,11-epoxy group and substituting a carboxymethoxy group for the 17-alpha-thioacetyl group. As a result of these structural changes, eplerenone has significantly increased selectivity for the mineralocorticoid receptor over other steroid receptors. Eplerenone is hepatically metabolized through the cytochrome system (CYP3A4) to inactive metabolites. The drug's elimination half-life is 4 to 6 hours. Concomitant administration of potent inhibitors of CYP3A4 (including ketoconazole, itraconazole, clarithromycin, erythromycin, verapamil, ritonavir, and others) may increase eplerenone concentrations and is therefore contraindicated. An eplerenone dose of 50 mg is approximately equivalent to 25 mg of spironolactone.[15]

Clinical Trials of Aldosterone Inhibitors in HF

The first major trial to demonstrate a beneficial effect of an aldosterone antagonist in HF was the Randomized Aldactone Evaluation Study (RALES).[16] This randomized, double-blind trial involved 1,663 patients with severe HF and a left ventricular ejection fraction (LVEF) of 35% or lower. Patients continued traditional therapy with ACEIs, loop diuretics, and, in most cases, digoxin. Patients received placebo or spironolactone 25 mg daily. The dose could be titrated upward to 50 mg or downward to 12.5 mg daily as tolerated. After an average follow-up of 24 months, the mean achieved dose was 26 mg daily. The relative risk for death with spironolactone was 0.7 (95% CI 0.6 to 0.82, $P < 0.001$). This 30% reduction in death was primarily attributed to decreases in the progression of HF and sudden cardiac death.

Hospitalizations for worsening HF were reduced 35% with spironolactone and more patients demonstrated improvement in NYHA classification (both $P < 0.001$).

Table 1: Detrimental Cardiovascular Effects Associated with Chronic Elevations in Aldosterone[7–9]

Hypernatremia
Hypokalemia
Hypomagnesemia
Impaired arterial compliance
Pressor effect
Decreased myocardial uptake of catecholamines
Ventricular arrhythmias
Increased production of plasminogen-activator inhibitor
Endothelial dysfunction
Baroreceptor dysfunction
Increased release of cytokines and other inflammatory mediators
Activation of macrophages
Stimulation of fibroblast and collagen production
Promotion of myocardial and vascular fibrosis
Promotion of ventricular and vascular hypertrophy and remodeling

Gynecomastia or breast pain in men occurred in 10% of spironolactone patients vs 1% of placebo patients. Despite the concomitant use of spironolactone and ACEIs, serious hyperkalemia was infrequent and not increased compared with placebo (2% vs 1%, $P = 0.42$). Likewise, there were no significant increases in serum creatinine compared with placebo. Overall, 8% of spironolactone patients discontinued treatment due to adverse effects compared with 5% in the placebo group.

RALES provided strong evidence for additional reductions in morbidity and mortality when an aldosterone inhibitor was combined with traditional HF therapy. The study findings, however, were limited to patients with severe HF (NYHA class III or IV). A major limitation of the study was the fact that only 11% of patients were receiving beta blockers, which are now considered standard therapy in this population. Although spironolactone was generally well tolerated, gynecomastia in men resulted in a higher rate of discontinuation compared with placebo (2% vs 0.2%, $P = 0.006$). This led investigators to speculate that the use of a selective aldosterone antagonist might maintain efficacy while minimizing drug-related adverse effects.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) addressed many of the concerns raised by RALES.[17] In this study, 6,642 patients were randomized to eplerenone (25 mg daily titrated to a maximum of 50 mg) or placebo. The study population consisted of patients who had experienced an AMI within 3 to 14 days and had a documented LVEF of 40% or less. Additionally, all study patients had signs of clinical HF or a history of diabetes.

Patients received standard HF therapy including ACEIs, ARBs, diuretics, and beta blockers. The mean follow-up was 16 months. The relative risk of death with eplerenone was 0.85 (95% CI 0.75 to 0.96, $P = 0.008$). A second primary endpoint, death from cardiovascular causes or hospitalization for cardiovascular events, was also reduced by eplerenone (RR 0.87, 95% CI 0.79 to 0.95, $P = 0.002$). Similar to what was seen in RALES, the reduction in cardiovascular death was primarily attributed to a lower rate of sudden cardiac death (21% risk reduction). Serious hyperkalemia (≥ 6 mmol/L) occurred in 5.5% of eplerenone patients compared with 3.9% of placebo patients ($P = 0.002$). Among males, there were no increases in either gynecomastia or impotence.[17]

EPHESUS provided additional evidence for the benefit of adding an aldosterone antagonist to standard heart failure therapy including beta blockers. Moreover, the benefit was achieved in patients with mild to moderate heart failure. Placebo mortality rates were 16.7% in EPHESUS compared with 46% in RALES, providing further evidence of the lesser severity of HF in the EPHESUS population. In addition, the problem of gynecomastia in male patients was overcome through the use of a selective aldosterone inhibitor with a lower affinity for progesterone and androgen receptors.

Serious hyperkalemia was reported more frequently with eplerenone in EPHESUS (5.5% vs 3.9% with placebo) compared with spironolactone in RALES (2% vs 1% with placebo). However, the attributed risk (drug–placebo) was comparable for the two trials. It is important to note that both RALES and EPHESUS excluded patients with baseline serum potassiums above 5. mmol/L or serum creatinines above 2.5 mg/dL. In EPHESUS, the risk of serious hyperkalemia was significantly increased in patients with a baseline creatinine clearance of less than 50 mL per minute (10.1% vs 5.9%, $P = 0.006$).

Clinical Guidelines

The most recent practice guidelines for the management of HF[5,6] provide limited recommendations for using aldosterone antagonists in patients with NYHA class IV HF, provided that renal function is adequate and serum potassium is normal. This limited recommendation was based on RALES, the only available evidence at the time these guidelines were developed. New guidelines that are expected later this year should address this issue more fully based on the findings of EPHESUS, which suggest benefit in patients with milder HF following AMI.

Cost Effectiveness

Because HF is a chronic progressive disease, drug therapy is life-long. As more drugs are shown to improve patient outcomes, the economic consequences must be considered. Data from RALES was used to evaluate the clinical outcomes and costs associated with the addition of spironolactone to standard HF drug therapy.[18] The study used a decision analytic model that incorporated outcomes from the first 35 months of RALES and cost data from the five countries

participating in the study. Based on this model, adding spironolactone increased the quality-adjusted life-years saved (QALYS) without increasing costs compared with placebo. In addition to improved survival, spironolactone improved functional status and lessened the burden of hospitalization.

The study findings were limited to the RALES population, which included only patients with severe HF. The findings from this analysis were not unexpected, given the positive findings of RALES and the low cost of spironolactone (AWP $0.46 to $0.88 per day). Because eplerenone is a new and relatively expensive drug (AWP $3.75 per day), similar economic analyses are urgently needed. An ongoing study is analyzing the quality of life and economic impact of adding eplerenone based on the EPHESUS findings.[19]

Implications for Practice

Findings from RALES and EPHESUS provide strong evidence of benefit when aldosterone antagonists are added to traditional HF therapy including beta blockers and ACEIs or ARBs. However, the limited clinical trial evidence, consisting of one major trial for each drug conducted in different HF populations, precludes definitive recommendations for one agent over the other in all HF patients. Strict adherence to evidence-based medicine would suggest that the drugs should be used in populations similar to the clinical trials in which they were evaluated. Thus, spironolactone would be the drug of choice for patients with severe HF (NYHA class III or IV). Conversely, patients who developed HF as evidenced by left ventricular dysfunction and symptoms of HF following AMI would be treated with eplerenone.

In some cases, however, patient-specific factors may override these guidelines. For example, when cost is a determining factor, spironolactone may be a more rational choice. In patients for whom drug interactions with P450 inhibiting drugs are a concern, spironolactone may again be the preferred drug. Conversely, in male patients who are concerned about sex-hormone adverse effects or those with a prior history of such adverse events, eplerenone would be the most appropriate choice. It should also be noted that neither drug has been adequately studied in the following HF populations: Patients with asymptomatic left ventricular dysfunction, patients with mild to moderate HF not associated with AMI, and patients with preserved systolic function. While it is tempting to theorize that the observed benefits in RALES and EPHESUS are a class effect that extends across the spectrum of HF, only controlled clinical trials can fully address these questions.

Regardless of which aldosterone antagonist is used, appropriate monitoring and counseling is essential. Serum creatinine and potassium should be assessed at baseline. Both spironolactone and eplerenone are contraindicated in patients with significant renal impairment (e.g., creatinine clearance 30 mL/min or less) or hyperkalemia (e.g., serum potassium > 5.5 mEq/L).

In accordance with the clinical trials, daily doses for both spironolactone and eplerenone should range between 25 mg every other day to a maximum of 50 mg daily. Dosage adjustments should be based on tolerance and serum potassium concentrations.

Based on the clinical trial protocols, serum potassium should be monitored minimally within the first week of therapy, at one month and periodically thereafter.[16,17] Any increase in potassium to greater than 5.5 mEq/L should trigger a concomitant medication review and a dosage reduction or alternate day therapy.

Patient drug profiles should be screened for drugs that inhibit CYP3A4. Concomitant use of these drugs with eplerenone is contraindicated. Additionally, patients should be counseled that grapefruit juice increases eplerenone concentrations by approximately 25%.[9]

Patients should be counseled to avoid potassium-containing supplements or salt substitutes unless prescribed and monitored by their physician. Patients with diabetes should be monitored more frequently. While the potential for drug-induced hyperkalemia with combination therapy has not been adequately studied in this population, diabetes alone appears to be a an independent risk factor for hyperkalemia.[20] Patients should also be cautioned to avoid nonprescription use of nonsteroidal antiinflammatory drugs (NSAIDs) without medical supervision, because these drugs may worsen renal function, raise blood pressure, and promote sodium retention.

Role of the Pharmacist

The relatively new indication for aldosterone antagonists in HF coupled with the limitations of the clinical trial data necessitates close attention and quality assurance assessments in this patient population. One study has reported inappropriate use of spironolactone relative to patient screening, monitoring, and the optimal use of other HF drugs including ACEIs and beta blockers.[21]

In addition, there have been several published reports of hyperkalemia associated with the use of spironolactone in HF.[15,22] Many of these reports resulted in hospitalization for renal dysfunction, renal dialysis, and, in some cases, death. However, further analyses of these cases reveals that most were associated with the use of doses higher than those used in the clinical trials, use in patients who would have been excluded from the trials, or inadequate potassium monitoring.[15] These concerns underline the need for pharmacists to take an active role in the care of these patients.

Conclusions

There is sufficient clinical trial evidence to recommend the addition of aldosterone antagonists to the armamentarium of drugs used to treat selected patients with systolic HF. In the absence of contraindications, all patients should first be placed on a beta blocker and an ACEI or ARB. Doses of spironolactone or eplerenone should be titrated to doses similar to those used in the clinical trials. The choice of aldosterone antagonist should be based on the severity of HF, history of recent AMI, and other patient-related factors including drug tolerance and costs.

Hopefully, future studies will more fully define the relative roles of spironolactone and eplerenone in the treatment of HF population and fully assess the comparative cost-effectiveness of these two drugs.

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Howard PA. The role of aldosterone antagonists in systolic heart failure. *Hosp Pharm* 2004;39:944-53.

Selected FDA Safety Alerts

Antidepressant Medications and Suicidality in Children and Adolescents

The Food and Drug Administration issued a Public Health Advisory, asking manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents, and additional information about the results of pediatric studies. FDA also informed these manufacturers that it has determined that a Patient Medication Guide (MedGuide), which will be given to patients receiving the drugs to advise them of the risk and precautions that can be taken, is appropriate for these drug products.

Avastin (bevacizumab)

FDA and Genentech, Inc. issued an important drug warning to healthcare providers that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to Avastin. The risk of fatal arterial thrombotic events is also increased. In randomized, active-controlled studies conducted in patients with metastatic colorectal cancer, the risks of a serious arterial thrombotic event was approximately twofold higher in patients receiving infusional 5-FU based chemotherapy plus Avastin, with an estimated overall rate of up to 5%. A revised Avastin package insert containing more detailed information on arterial thromboembolic events is in development. The current Avastin package insert is provided below.

Effexor (venlafaxine HCl)
Effexor XR (venlafaxine HCl)

FDA and Wyeth Pharmaceuticals notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of labeling to alert healthcare providers of two important safety issues.

Neonates exposed to Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester of pregnancy have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery.

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The warning recommends patients being treated with antidepressants be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.

Geodon (ziprasidone)

FDA and Pfizer notified healthcare professionals of revision to the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking Geodon. FDA has asked all manufacturers of atypical antipsychotic medications, including Pfizer, to add this Warning statement to labeling.

Levoxyl (levothyroxine sodium)

FDA and King Pharmaceuticals notified healthcare professionals of revisions to the PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections of labeling, describing reports of choking, gagging, tablets stuck in throat and dysphagia while taking Levoxyl. These reports have predominately occurred when Levoxyl tablets were not taken with water. It is recommended that Levoxyl tablets be taken with a full glass of water.

Lovenox (enoxaparin sodium injection)

FDA and Aventis Pharmaceuticals revised the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of labeling, describing the need for a dosage adjustment for patients with severe renal impairment (creatinine clearance <30mL/min) who have increased exposure to enoxaparin. No specific dosage adjustment is required in patients with mild or moderate renal impairment and in low-weight patients. However, low-weight patients should be observed carefully for signs and symptoms of bleeding.

Paxil (paroxetine hydrochloride) Tablets
Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

FDA and GlaxoSmithKline notified healthcare professionals of revisions to the WARNINGS and PRECAUTIONS sections of labeling to alert healthcare professionals that patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The warning recommends patients being treated with antidepressants be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.

Remicade (infliximab)

FDA and Centocor notified healthcare professionals of revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information for Remicade, indicated for the treatment of rheumatoid arthritis and Crohn's disease. Cases of leukopenia, neutropenia and pancytopenia, some with fatal outcome, and cases of CNS manifestation of systemic vasculitis, were described in patients receiving Remicade. The ADVERSE REACTIONS section was updated to include neutropenia, pericardial effusion and systemic and cutaneous vasculitis. In controlled studies of all TNFα-blocking agents, including Remicade, more cases of lymphoma have been observed among patients receiving the agents than among control group patients. Malignancies have also been observed in open-label, uncontrolled clinical studies at a rate several-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. FDA has recommended a warning concerning malignancy be added to the labeling for all therapeutic agents that block TNF.

Reminyl (galantamine hydrobromide)

FDA, Janssen Pharmaceutica Products, and Johnson & Johnson Pharmaceutical Research & Development notified healthcare professionals of reports of medication errors involving confusion between Reminyl, a drug approved for the treatment of mild to moderate dementia of the Alzheimer's type, and Amaryl (glimepiride), a product of Aventis Pharmaceuticals, indicated for the treatment of non-insulin dependent (Type 2) diabetes mellitus. These reports include instances in which Reminyl was prescribed but Amaryl was incorrectly dispensed and administered instead, leading to various adverse events including severe hypoglycemia and one death.

Risperdal (risperidone)

FDA and Janssen revised the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking Risperdal. MedWatch is posting a revised version of a letter originally distributed to health care professionals November 2003. FDA asked all manufacturers of atypical antipsychotic medications, including Janssen, to add this Warning statement to labeling.

Rituxan (rituximab)

Biogen Idec and Genentech notified healthcare professionals of revisions to the WARNINGS section of the prescribing information due to reports of Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death in some patients with hematologic malignancies. Persons at high risk of HBV infection should be screened before initiation of Rituxan. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following Rituxan therapy.

Serzone (nefazodone hydrochloride) Tablets

FDA and Bristol-Myers Squibb notified healthcare professionals of revisions to the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and WARNINGS sections to encourage healthcare providers to engage in a thorough risk–benefit analysis, including consideration of the risk of hepatic failure associated with Serzone treatment, when deciding among alternative treatments available for depression. In addition, healthcare providers and consumers are cautioned about the need for close observation of patients being treated with antidepressants for clinical worsening of the symptoms of depression, for the emergence of suicidality, and for the emergence of a variety of other symptoms that may represent a worsening of the patient's condition.

Vioxx (rofecoxib)

Merck & Co., Inc. announced a voluntary withdrawal of Vioxx (rofecoxib) from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx. Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms, and was later approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

Zometa (zoledronic acid) Injection

FDA and Novartis notified healthcare professionals of revisions the PRECAUTIONS and ADVERSE REACTIONS sections of labeling, describing spontaneous reports of osteonecrosis of the jaw mainly in cancer patients, who have received bisphosphonates as a component of their therapy. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

Note: **Detailed information on these and other FDA safety alerts is available via the FDA homepage (*www.fda.gov*).**

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

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